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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,236	11/04/2003	Stanley T. Crooke	ISIS-5207	5280

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
06/22/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,236	CROOKE, STANLEY T.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,71-73 and 76-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,71-73,76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

In view of the Pre-Appeal Brief and conference the finality of the rejection of the last Office action filed 12/09/2009 is withdrawn.

Applicant's response has been considered. Rejections and/or objections not reiterated from the previous office action are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 71-73 and 76-79 are pending in the application.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 71-73 and 76-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Monia et al. (Journal of Biological Chemistry 1993, vol. 268, pages 14514-14522), Manche et al. (Molecular and Cellular Biology 1992, of record) and Baracchini et al. (US 5,801,154, of record).

The claims are directed to compositions comprising a duplex comprising 17 to 25 linked nucleotides in length wherein at least one strand comprises a plurality of 2'-hydroxyl pentofuranosyl sugars. In specific embodiments the strands of the duplex comprise gapmers and further comprise a 2'-sugar or phosphorothioate linkages. While not specifically recited, as set forth in the earliest priority document that provides written description support for the claimed subject matter (US 6,107,094, example 27a) these duplexes are artificial substrates for RNase enzymes that are useful for testing activity of such enzymes.

At the time the invention was made, those in the art routinely synthesized short duplexes containing ribonucleotide residues for the purpose of studying the activity and structural requirements of different enzymes. This is demonstrated by the teachings of Wyatt et al., Monia et al. and Manche et al.

Wyatt et al. teach that sensitivity of DNA and RNA to nucleases depends upon both chemical and conformational differences. For example, the 2'-OH makes ribonucleotides susceptible to alkaline hydrolysis and cleavage by ribonucleases, a mechanism not available for cleavage of deoxynucleotides. Wyatt et al. further teach that RNase V1 from cobra venom is a widely used probe for double-stranded RNA that does not have a specific requirement for 2'-OH and is thus postulated to be like RNase H, which cleaves RNA-DNA duplexes. In order to probe the structural requirements of RNase V1 and RNase H, Wyatt et al. synthesized a series of 14 nucleotide duplexes wherein 2'-deoxyribonucleotides were site-specifically incorporated to allow study of duplexes containing covalently linked deoxy and ribo-nucleotides. These duplexes

contain a sequence complementary to the ADCK2 gene (GenBank accession number NM_052853.3).

Monia et al. teach that susceptibility of unmodified phosphodiester oligonucleotides to nucleolytic degradation has made them unattractive molecules for oligonucleotide therapeutics. Chemical modifications have been introduced into oligonucleotides to increase their resistance to nucleolytic degradation, but these modifications can also possess additional properties that limit their usefulness, such as weaker affinity for RNA targets. Monia et al. performed a systematic study in which chimeric oligonucleotides containing various 2' sugar modifications were characterized for hybridization affinity and ability to direct target RNA cleavage by mammalian RNase H in order to study how to take advantage of the beneficial properties of oligonucleotide modifications while maintaining enzymatic substrate requirements. Monia et al. synthesized a 17-mer phosphorothioate having complementarity to Ha-ras for structure-function analysis of 2'-sugar modifications. These oligonucleotides were analyzed for hybridization affinity to a 25 nucleotide complementary RNA (see figure 2) and these short duplexes were additionally analyzed for their ability to activate RNase H *in vitro* using HeLa cell extracts (see pages 14516-17 and materials and methods "RNase H analysis").

Manche et al. teach that the protein kinase DAI, the double-stranded RNA-activated inhibitor of translation, is a pivotal cellular regulatory enzyme that is an important element in the host antiviral response. Despite its importance as a regulatory enzyme, the interactions between DAI and its RNA effectors were complicated and

incompletely understood. To better understand these interactions Manche et al. analyzed interaction of the enzyme with RNA duplex molecules of specified sizes ranging from 15-104 nt (see figure 1) in order to study binding and protection of dsRNA as well as activation and inhibition of the kinase.

At the time the instant application was filed those of ordinary skill in the art were familiar with the drawbacks of using nucleic acids in cellular environments or under conditions simulating such environments (particularly nucleolytic degradation as noted by Monia et al.) and were also familiar with antisense oligonucleotides used for research purposes.

Baracchini et al. provide additional teachings of the state of the art regarding use of modified nucleotides. Baracchini et al. teach that preferred oligonucleotides for use in cellular environments are modified in their sugar, backbone linkage and nucleobase composition and that such modifications have desirable properties such as enhanced target affinity and increased stability in the presence of nucleases. One particular type of modified oligonucleotide described at column 8 is chimeric oligonucleotides, including gapmers. Baracchini et al. further teach that common sugar substituents include morpholino or peptide nucleic acid and further teach the use of phosphorothioate linkages.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make short duplex compounds that contain RNA residues and 2'-Omethyl modified nucleotides. Based on the teachings of Wyatt et al., Monia et al. and Manche et al., the person of ordinary skill would have reason to make short duplex

oligonucleotides containing RNA residues and modified nucleotides for the purpose of studying enzyme structure and activity and would recognize that these duplexes could be made of various lengths, depending on the requirements of the particular enzyme being studied, for example, Monia et al. provide an explicit teaching of an artificial enzyme substrate comprising 17 and 25 nucleotide strands. Based on the teachings of Monia et al. and Baracchini et al, the person of ordinary skill in the art would have reason to incorporate 2'-sugar groups into the duplex because these references teach that nucleolytic degradation is a problem for nucleic acids and that stabilization of a duplex with modified nucleotides provide resistance to nucleases. Based on the knowledge available to the person of ordinary skill of the ways to incorporate modified nucleotides (including gapmer structures) and the usefulness of modified nucleotides in providing nuclease stability and binding affinity that is provided by the teachings of Monia et al, and Baracchini et al., the person of ordinary skill would be motivated to use these known modifications and modification patterns as a starting point for optimizing the stability and affinity of short duplexes. The person of ordinary skill in the art would be able to predictably make duplex sequences comprising the claimed modifications at any desired position because these modifications and methods of nucleic acid synthesis are well known and routinely used by those in the art.

Thus, the invention of claims 1, 71-73 and 76-79 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants' arguments in the re-appeal brief of 04/07/10 are moot in view of the newly applied grounds of rejection.

Claim Rejections - 35 USC § 103 - withdrawn

The rejection of claims 1, 71-73 and 76-79 under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Cell 1993 of record), Manche et al. (Molecular and Cellular Biology 1992 of record), Agrawal et al. (WO 94/01550, cited on IDS of 4/4/05) Baracchini et al. (US 5,801,154 of record) and Acevedo et al. (US 5,519,134 of record) is withdrawn in view of the newly applied grounds of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Fereydoun Sajjadi at 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1635